Two-year outcome of juvenile idiopathic arthritis in current daily practice: what can we tell our patients?

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Abstract

Objectives

This paper aims to evaluate disease course and outcome of patients in the first 2 years after diagnosis of juvenile idiopathic arthritis (JIA) when treated according to local standard of clinical care, focusing on achievement of inactive disease, functional ability and radiological joint damage.

Methods

A retrospective inception cohort study of children with JIA, diagnosed between January 2003 and June 2007 and treated in referral centres in Amsterdam, was carried out. Disease status was determined for every outpatient-clinic visit. Data regarding medication, functional outcome and radiography were recorded.

Results

One hundred and forty-nine consecutive newly diagnosed JIA patients were included. Median age at diagnosis was 11.8 years; median follow-up was 33 months. Synthetic DMARDs (sDMARDs) were used by 95% of patients, including methotrexate in 85%, sulfasalazine in 41% and biologics in 20%. sDMARDs were started within median 1 month after diagnosis. During follow-up, 77% of patients achieved a total of 244 episodes of inactive disease (ID). ID was reached after median 10 months. No baseline predictive factors for achievement of ID could be identified. After 2 years a median CHAQ score of 0.6 was reported. Radiological joint damage occurred at some point in 18 patients (12%); 10 of these patients developed erosions within median 20 months after their first clinic visit.

Conclusion

With current management strategies in daily clinical practice, 77% of newly diagnosed JIA patients achieved a first episode of inactive disease within a median of 10 months. After 2 years, patients reported moderate functional disability and more than 10% showed radiological evidence of joint damage.

Key words

arthritis, juvenile rheumatoid / radiography, arthritis, juvenile rheumatoid / drug therapy, treatment outcome, functional ability, daily clinical practice

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Introduction

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory arthritis, persisting for over 6 weeks, with an onset before the age of 16. No specific laboratory tests define JIA. It is an umbrella diagnosis covering various types of inflammatory arthritis which can follow a heterogeneous course.

JIA is considered a common cause of irreversible joint damage originating in childhood. According to the classification of the International League of Associations for Rheumatology (ILAR), 7 different categories of JIA are defined based on clinical and laboratory findings (1). Despite accumulating knowledge of the disease and increasing treatment options, most JIA patients show relapsing or persistent disease activity. JIA is commonly active in adulthood, leading to joint function impairment, joint destruction and decreased quality of life (2).

In several studies, the long-term outcome of JIA has been described, but since treatment options in JIA are quickly developing, none appears fully applicable to inform our newly diagnosed JIA patients about the expected course of their disease (2-6).

Until now, no treatment strategy has been demonstrated to be the most effective to achieve disease remission in the majority of patients (7). Adjacent to NSAIDs, systemic corticosteroids and intra-articular corticosteroid injections, agents such as methotrexate (MTX) and sulfasalazine (SSZ) (synthetic disease modifying anti-rheumatic drugs, sDMARDs) and biologic agents (also called biologic DMARDs) such as the tumour necrosis factor inhibitors (anti-TNF-alpha) have a place in the treatment of JIA, used either as monotherapy or in combination. Evidence-based standards of treatment do not exist in the Netherlands (8). Guidelines are being developed, and recently the American College of Rheumatology (ACR) has published treatment recommendations. Although these recommendations are largely expert opinion-based, they may serve as a reference for clinicians (9).

Recent studies have shown that the disease activity pattern shortly after the diagnosis of JIA is predictive for the clinical course in the following years and may relate even better to long-term disease outcome than disease characteristics at onset (4, 10-14).

The goal of the present study was to evaluate disease course and outcome in the first 2 years after the diagnosis of JIA, especially focusing on achievement of inactive disease, functional ability and radiological joint damage in JIA patients visiting the paediatric rheumatology outpatient clinics in 2 referral centres in Amsterdam, the Netherlands, when treated according to local standards of clinical care.

Materials and methods

Patients

Between January 2003 and June 2007, 164 patients were newly diagnosed with JIA. Of these 164 patients, 15 patients were excluded because of missing data or loss to follow-up.

The remaining inception cohort of 149 JIA patients of the outpatients' clinic dedicated to paediatric rheumatology in the Emma Children's Hospital/Academic Medical Centre and Reade (location Jan van Breemen Institute) in Amsterdam was analysed retrospectively. Both centres contributed equally and 52 patients were seen in both centres. Patients were seen every 3 months or more often when the disease was very active. At the time of data entry, all patients had a follow-up duration of minimally 1 year. All 7 categories of JIA according to the ILAR classification were included. The study was performed according to the regulations of the medical ethical committees of the institutes.

Treatment

Therapeutic decisions were made by the treating paediatric rheumatologist based on clinical findings, applying the standard of anti-rheumatic treatment in the Netherlands. This treatment strategy consists of a sequential regimen as to sDMARDs, followed by a step-up regimen as to the addition of biologic agents. Patients had full access to all anti-rheumatic drugs available in the Netherlands, including biologics.

Data collection

The patient records were reviewed and all changes in disease activity during the complete follow-up were recorded. The following parameters were used to describe the disease status: state of disease activity (active or inactive), the subjective physicians' global assessment of disease activity (scored on a 5 points scale [0=inactive disease, 1=mild, 2=moderate, 3=severe 4=very severe]) and the number of joints with arthritis (referred to as clinical severity index and categorised as: 0=no joints, 1=monoarthritis, 2=oligoarthritis [2–4 joints], 3=polyarthritis [5–10 joints], 4=severe polyarthritis [>10 joints], and in case of systemic JIA an additional category 5=systemic features). The charts contained joint counts described in a standardised manner. However, due to the retrospective nature of this study, a summarised score was found more applicable. Active arthritis was defined as a joint with swelling not due to bony enlargement or, if no swelling was present, limitation of motion accompanied by either pain on motion and/or tenderness (7).

For each visit, data were recorded to determine the inactive disease (ID) criteria as defined by Wallace *et al*. (7): absence of active arthritis, no systemic features, no uveitis, a physicians' global assessment indicating inactivity (category 0) and normal erythrocyte sedimentation rate (ESR). Because laboratory tests were not performed at every clinic visit, ESR was not required for ID classification if the patient otherwise met ID criteria. Data on ESR were missing in 3% of patients classified as having ID. Each patient could have multiple subsequent episodes of active and inactive disease. Episodes of ID were analysed to identify patients achieving clinical remission on and off medication (7).

The Childhood Health Assessment Questionnaire (CHAQ) score was used to evaluate functional disability; pain and wellbeing were assessed by visual analogue scales (VAS 0–100) (15).

Besides data concerning disease-activity, data regarding gender, age, ethnicity, duration of symptoms prior to first clinic visit, laboratory results, imaging data and medication dosage adjustments as well as start- and stop dates were recorded. All data from conventional radiographs obtained at diagnosis and during follow-up were collected. Imaging reports were provided by paediatric musculoskeletal radiologists. Radiologic damage was defined as the presence of erosions; erosions were defined as disruption of the cortical surface of any size.

Rheumatic factor (IgM-RF), anti-cyclic citrullinated peptide antibodies (anti-CCP) and anti-nuclear antibodies (ANA) were routinely measured ≥2 times and scored positive if there were 2 positive results at least 3 months apart.

Statistical analysis

Descriptive statistics were reported as absolute frequencies or as median values with an inter-quartile range (IQR). We compared disease outcome and sDMARD treatments between the JIA categories. Depending on the tested variable, Kruskal Wallis, Mann-Whitney U- and chi-square tests were used for comparisons of medians and proportions. A p-value <0.05 was considered statistically significant. To find out whether ANA-status, CHAQ-score (dichotomised in 2 categories <0.75 and ≥0.75, with 0.75 being the cut-off point for patients with moderate to severe disability) (14, 16), diagnosis, disease duration and severity-index at initiation of sDMARD therapy were associated with the achievement of inactive disease and remission on and off medication, logistic regression was performed. SPSS (Chicago, IL, USA) version 17.0 was used for all analyses.

Results

Patient characteristics

Data from 149 patients with definite JIA diagnosed within the inclusion period were analysed. The patient characteristics are shown in Table I. Median follow-up was 32.5 months (IQR 21.0–46.0 months). Median diagnostic delay was 7 months (IQR 3–19). Age at diagnosis was lower in the persistent oligoarthritis category (median 9 years [IQR 7–13 years]) and higher in the rheumatoid factor (RF)-negative polyarthritis category (median 16 years [IQR 14–17 years]).The 3 RF positive patients were positive for anti-CCP as well; the other 2 anti-CCP positive patients were classified as RF-negative polyarticular JIA. HLA-B27 was tested positive in 16 out of 119 patients (13%), including 8 out of 13 (62%) patients with enthesitis related arthritis (ERA).

Uveitis was diagnosed in 7 patients during the observation period, 1 of these patients was ANA positive (14%). In 10% of the patients, data on ophthalmologic screening were not available.

Medication use

All but 1 patient used NSAIDs during the observed period. DMARDs including biologics were used on a regular

Table I. Patients' characteristics.

Characteristics	n (%)
Clinical characteristics	
Female	98 (66)
Age at diagnosis JIA (years)	
<8	36 (24)
8–12	38 (26)
12–14	37 (25)
>14	38 (26)
Uveitis	7/134 ¥ (5)
Ethnicity	
Caucasian	132 (89)
Other*	15 (10)
Unknown	2 (1)
Median disease duration (IQR) in months	32.5 (21.0–46.0)
Median time to diagnosis (IQR) in months	7.0 (3.0–19.0)
Laboratory characteristics	
ANA positive¥¥	40/149¥ (27)
RF positive**	3/149¥ (2)
Anti-CCP positive	5/ 147¥ (3)
HLA B27 positive	16/119¥ (13)
JIA categories (% of total)	
Persistent oligoarthritis	19 (13)
Extended oligoarthritis	14 (9)
RF-negative polyarthritis	81 (54)
RF-positive polyarthritis	3 (2)
Systemic JIA	1 (1)
Undifferentiated JIA	13 (9)
Psoriatic arthritis	5 (3)
Enthesitis related arthritis	13 (9)

*Other ethnicities: Asian, Caribbean. **The presence of IgM rheumatoid factor on at least 2 occasions at least 3 months apart. ¥ Number of patients for whom data were available. ¥¥ At least 2 positive results of ANA determination at a titer ≥1:160 at least 3 months apart.
JIA: juvenile idiopathic arthritis; IQR: inter-quartile range; ANA: antinuclear antibodies; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide.

Table II. Clinical severity index at start of first sDMARD treatment (n=141).

Number of joints with arthritis	n (% of patients initiating sDMARD)
Monoarthritis	17 (12)
Oligoarthritis	37 (26)
Polyarthritis	61 (43)
Severe polyarthritis	25 (18)
Systemic features	1 (1)
Total	141

*p-value=0.001 (chi-Square).
sDMARD, synthetic disease modifying anti-rheumatic drug.
Monoarthritis: 1 joint; oligoarthritis: 2–4 joints; poly-arthritis: 5–10 joints; severe poly-arthritis: >10 joints.

basis by 95% of patients. Etanercept was the most frequently prescribed biological and was used by 27 (18%) of patients. In all but 1 patient, etanercept was added to MTX treatment and was started median 15.0 months (IQR 11.0–28.0) after diagnosis. In 9 of these patients this was done after inefficacy of previous SSZ-treatment.

sDMARD treatment (either MTX or SSZ) was initiated median 1 month (IQR 0–3 months) after diagnosis. The clinical severity index at the time of introduction of the first sDMARD treatment is shown in Table II. sDMARD treatment was started in 141 patients, of whom 54 (38%) had active arthritis in 4 or fewer joints at the time of initiation; 32 of these 54 patients developed a polyarticular course. MTX was started as first sDMARD relatively more often in patients with severe polyarthritis compared to SSZ (of all patients starting sDMARD treatment for severe polyarthritis, 84% started MTX).

Almost all patients (82%) who started etanercept treatment had polyarthritis, including 57% with severe polyarthritis (defined as >10 active joints).

The mean prescribed treatment dosage of MTX was 20.1 mg (range: 7.5–35.0 mg once a week), equaling 14.7 mg/m2 (range 6.5–24.5 mg/m2). The maximum dose of MTX treatment was reached after a median build-up period of 6.0 months, (IQR 1.0–13.3 months). All patients initially started MTX treatment orally and some changed to subcutaneous administration for various reasons.

Of the 58 patients who started SSZ as their first sDMARD, 43 (74%) switched to MTX later in the disease course because of ineffectiveness or adverse events. Switching from SSZ to MTX occurred after a median of 5.0 months after start of SSZ (IQR 3.0–8.0). Three of the 83 patients initiating MTX switched to SSZ, because of severe aversion against MTX. Table III shows the reasons for cessation of sDMARDs. MTX was stopped in 18% (23/126), whereas SSZ was discontinued in 80% (49/61) of patients. The most common reason for cessation of SSZ was ineffectiveness (51%), whereas severe aversion against the drug prevailed in MTX-users (10%). Discontinuation of MTX occurred after a median treatment period of 18 months (IQR 13.0–23.0 months). Discontinuation of SSZ treatment occurred after a median treatment duration of 7 months (IQR 4.0–13.3). Adverse events that were considered serious enough by the clinician to break off treatment with SSZ included: skin reactions (in 3 patients), hypersensitivity (1 patient), headaches and concentration problems (1 patient), liver biochemistry test elevations (2 patients) and leucopoenia (1 patient). All symptoms disappeared completely shortly after cessation of treatment. Six SSZ treated patients (10%) decided to discontinue treatment because of resistance against medication use in general. Etanercept was discontinued by 3 of the 27 treated patients. Two patients discontinued treatment because of ineffectiveness and 1 patient stopped etanercept usage after achieving ID.

Systemic glucocorticoids were started in 19 patients, 12 of whom were diagnosed within the RF-negative polyarticular category. In all cases, glucocorticoids were added at start of other DMARDs for a bridging effect. The mean dosage prescribed was 13.3 mg (range 2.5–42.5 mg), equalling 0.24 mg/kg/day (range 0.09–1.00 mg/kg/day). The mean duration of treatment was 2.0 months (IQR 0.9–9.2).

Table III. Reasons for stopping sDMARD treatment.

Reason for stopping sDMARD	MTX (n=126 patients)		SSZ (n=61 patients)	
	n (% of total group of patients receiving MTX)	Median time to cessation MTX in months (IQR)	n (% of total group of patients receiving SSZ)	Median time to cessation SSZ in months (IQR)
Remission	3 (2)	16.0 (8.0–21.0)	4 (7)	28.5 (17.1–40.6)
Adverse event	3 (2)	17.0 (14.0–18.0)	8 (13)	0.8 (0.6–4.0)
Aversion	12 (10)	22.0 (17.5–37.5)	–	–
Ineffectiveness	–	–	31 (51)	8.9 (6.5–11.7)
Other	5 (4)	13.0 (2.0–19.5)	6 (10)	4.5 (3.0–23.7)
Total	23 (18)	18.0 (13.0–23.0)	49 (80)	7.4 (4.6–13.1)

Other reasons for stopping included resistance against long-term use of medication.
sDMARD: synthetic disease modifying anti-rheumatic drug; MTX: methotrexate; SSZ: sulfasalazine; IQR: inter-quartile range.

Table IV. JIA category and time frame for patients to reach inactive disease.

JIA category	n of patients (% within category)	Median months to reach inactive disease (IQR)
Persistent oligoarthritis	18 (95)	7.0 (4–13)
Extended oligoarthritis	11 (79)	3.0 (1–13)
RF negative polyarthritis	57 (70)	12.0 (8–19)
RF positive polyarthritis	0 (0)	–
Systemic JIA	0 (0)	–
Undifferentiated JIA	11 (85)	10.0 (6–18)
Psoriatic arthritis	5 (100)	8.0 (6–13)
Enthesitis related arthritis	13 (100)	17.0 (5–20)
Total	115 (77)	10.0 (6–17)

Inactive disease as defined by Wallace *et al*. (7).
RF:rheumatoid factor; JIA: juvenile idiopathic arthritis; IQR: inter-quartile range.

Inactive disease

During the follow-up period, 115 patients (77% of the total cohort) achieved a total of 244 episodes of inactive disease (ID) (Table IV). Of these 115 patients, 91 (79%) had a subsequent episode of active disease. The other 24 patients were still in an inactive disease state at the last recorded visit. The median period to achieve a first period of ID was 10 months (IQR 6.0–17.0 months). The median duration of ID of the 91 patients that had a subsequent active episode was 17 weeks (IQR 12.0–35.0). Of the 115 patients achieving ID, 48 achieved disease remission on medication and 4 patients achieved disease remission off medication during 1 of their ID episodes. Patients achieving remission on or off medication did not differ from patients only achieving ID with regard to age, ANA status, diagnosis or gender.

Follow-up duration was longer for patients achieving ID compared with patients not achieving ID (Kruskal-Wallis test, $p<0.001$). ANA-status, age at onset, gender, diagnosis nor severity index at start of DMARD treatment were associated with achievement of ID. These findings did not change when corrected for follow-up duration.

In Table V, the medication use at the first episode of ID is shown. ID was reached by 19 patients using solely an NSAID. All except 1 patient had a relapse of arthritis. This patient reached ID in the last follow-up visit. When arthritis relapsed, intra-articular corticosteroid injections (IAS) and/or DMARDs were added in all but 2 patients. A state of ID was reached by 5 patients after treatment with IAS only. In all of these patients arthritis recurred after a median of 16 weeks.

The majority of patients (91/115; 79%) reached a first episode of ID while on sDMARD treatment. Of the 67 patients on MTX, 19 had previously unsuccessfully been treated with SSZ.

Functional disability

Functional disability was recorded for 71 patients (48% of total cohort) at median 39 months (IQR 28–50 months) after diagnosis. The group of patients that filled out the CHAQ were similar to the remaining patients as to sex and JIA category, but they were significantly younger at diagnosis and at the moment CHAQ was filled out ($p<0.001$ Mann-Whitney U-test).

The median CHAQ score was 0.63 (IQR 0.25–1.38). Moderate to severe disability (CHAQ score ≥0.75) was reported by 34/71 of patients (48%). Pain and general wellbeing assessed by means of a VAS score (0–100) showed a median score of 22 (IQR 1–55) and 24 (IQR 7–56), respectively. Not achieving ID in the observed follow-up period was associated with moderate to severe disability (CHAQ scores [≥0.75]) after a median of 39 months (OR 6.89, 95%CI [1.57–30.20], corrected for disease duration at CHAQ measurement and follow-up duration). We added this finding to the results section.

Radiological damage

Radiographs were available for all patients. A total of 130 (87%) patients had conventional radiographic imaging within 6 months before or after diagnosis and 114 (77%) had radiographs taken at some point during follow-up.

Radiographic evidence of joint damage in the form of erosions was detected in 18 patients (12%) at some point during their follow-up. Erosions were present in 8 of the 130 patients (6%) who had radiographic imaging within 6 months before or after diagnosis. The remaining 10 patients developed erosions in a median of 23 months after their first clinic visit (IQR 11–35 months). Erosions occurred in hands or wrists in 6 patients, in feet in 4 patients, in knees in 3 patients, ankles in 3 patients, shoulders in 1 patient, SI-joints in 3 patients, and hips in 1 patient.

Table V. Medication use adjacent to first episode of inactive disease (n=115).

Medication	n (% of total number of patients who reached inactive disease)
NSAID alone	19 (17)
Intra-articular corticosteroid injection	5 (4)
Methotrexate	67 (58)
Sulfasalazine	24 (21)
Etanercept	10 (9)

Intra-articular corticosteroid injection, methotrexate and sulfasalazine were always taken in combination with an NSAID, except for 1 patient. Etanercept was always prescribed in combination with an sDMARD. At the first episode of inactivity, no other sDMARDs or biologic agents were used.

Discussion

This study shows that in daily clinical practice the majority of newly diagnosed JIA patients achieve a period of ID within 2 years after the diagnosis. For a considerable proportion of patients, however, our current treatment strategies are insufficient to reach this goal. Functional disability was moderate median 39 months after diagnosis. Patients achieving ID within the observed period reported lower CHAQ scores than patients not achieving ID. Radiologic joint damage in the form of erosions was present in over 10% of patients.

Polyarticular JIA patients were overrepresented in the present study compared with other study-cohorts. Furthermore, our oligoarticular patients were older at disease onset compared to the other studies (17-21). These differences may be caused by referral bias, as our study cohort is derived from tertiary referral centres. Presumably, patients within the oligoarticular categories are more often treated by general paediatricians or rheumatologists rather than by specialised paediatric rheumatologists. The patients described in our study seem to represent the more severe end of the spectrum within the heterogeneous diagnosis of JIA.

Another notable finding is the low prevalence of uveitis (5%). This may be related to relatively early start of sDMARDS treatment and the only 2-year duration of follow-up. Uveitis may develop later in the disease course (22).

Concerning the achievement of inactive disease, our results are partly in line with those reported in other studies. Wallace *et al*. described a cohort of JIA patients with more than 4

years of follow-up, in which 89% of patients achieved ID after a median of 15 months (21). Achievement of ID was positively associated with the oligoarticular subtype. Comparison of these results with our study-cohort is hampered by the fact that our cohort included a significant lower number of persistent oligoarticular patients.

A more recent study by Ringold *et al*. described a cohort of only polyarticluar patients followed for an average of 30 months (23). In this study, 78% of the patients achieved ID within the first year, whereas in our cohort 75% of patients achieved ID within 17 months. This difference may be explained by an even more aggressive treatment strategy compared to ours with earlier introduction of biologic therapy in the Ringold *et al*. cohort resulting in earlier ID.

ANA-status has been described as a potential classifying factor for JIA, instead of the number of involved joints at onset. It is suggested that the ANA status identifies a more homogeneous subgroup of JIA patients (24-25). In our study, we did not find an association of ANA status with the achievement of ID, which is consistent with 3 other cohort studies (19, 21, 23). Nordal *et al*. (19) found an association of age at onset with achievement of ID; this we could also not confirm.

The ID-rate after intra-articular corticosteroids in the present study is low (26). This may be due to the high prevalence of polyarticular JIA and the treatment strategy to inject only a maximum of 2–3 large joints per patient.

Early introduction of an sDMARD and subsequently lower disease activity scores are known to have a positive effect on long-term outcome (10-12, 14, 27-28) In our study, sDMARDs were introduced median 1 month after diagnosis. The proportion of patients treated with SSZ is relatively high compared with other study-cohorts. SSZ has proved to be moderately effective in the treatment of JIA, and may be especially beneficial in the ERA category, as is described in the recently published ACR JIA treatment recommendations (9, 29-30). At the moment however, MTX is the preferred initial sDMARD in all other non-systemic JIA categories, because of its proven efficacy and its good safety profile. In our study, 51% of patients treated with SSZ discontinued treatment because of ineffectiveness, compared to none of the initially MTX-treated patients. When the arthritis does not respond to SSZ, there is the option to switch to MTX; whereas persisting arthritis during MTX treatment can be handled with modifications such as dose increase, change of administration route or addition of biologic treatment. Due to local reimbursement regulations, addition of biologics to SSZ without failure of MTX treatment was not allowed. With regard to achievement of ID, no association between the type of first sDMARD treatment and time of achievement of ID was detected.

Safety profiles for SSZ and MTX were comparably good. Relatively few adverse events occurred during SSZ treatment, especially when compared to the reported number of adverse events in the placebo-controlled SSZ-trial by Van Rossum *et al*. (30) This might be related to the stricter rules for reporting of adverse events and cessation of treatment in clinical trials compared to daily practice. The 13% adverse event rate of SSZ observed in the current study is comparable with other open-label SSZ studies reporting adverse event rates ranging between 11–17% (31-32). Severe aversion was the most important adverse event during MTX treatment, resulting in a 10% discontinuation rate. This side-effect appears to be common and difficult to reverse (33-34).

A number of potential limitations to our study must be acknowledged, the first being the retrospective design. A retrospective study is subject to missing and possibly erroneous data. We cannot account for changes in disease state in between clinic visits. For the identification of inactive disease in this study, we relied on clinical examination and laboratory findings reflecting daily clinical practice.

The radiological damage that we report may be underestimated, since we focused on erosions on conventional radiographs. We did not take other imaging modalities into account, which may be more sensitive in detecting earlier forms of joint damage (35-36). Furthermore, selection bias may have been introduced by inconsistent radiographic follow-up. Possibly, the physician saw a higher need for radiographic follow-up in the more severely affected patients.

Routine use of CHAQ was implemented in the studied clinics only after data collection had finished, therefore data on functional disability are limited and may be skewed to the more severely affected patients.

In conclusion, our study shows that newly diagnosed JIA patients can expect intensive treatment, at least during the first 2 years of their disease, resulting in inactive disease in 77% of the patients. As our cohort consisted largely of patients with polyarticular course JIA, these results are mostly applicable to this patient group. Radiological joint damage may occur in a significant number of patients and functional ability may become moderately impaired. There is room for treatment improvement. Therefore, studies identifying the optimal treatment strategy leading to an earlier and longer state of inactive disease are desirable.

References

1. PETTY RE, SOUTHWOOD TR, MANNERS P *et al*.: International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004; 31: 390-2.
2. ADIB N, SILMAN A, THOMSON W: Outcome following onset of juvenile idiopathic inflammatory arthritis: II. predictors of outcome in juvenile arthritis. *Rheumatology* (Oxford) 2005; 44: 1002-7.
3. MINDEN K, NIEWERTH M, LISTING J *et al*.: Long-term outcome in patients with juvenile idiopathic arthritis. *Arthritis Rheum* 2002; 46: 2392-401.
4. OEN K: Long-term outcomes and predictors of outcomes for patients with juvenile idiopathic arthritis. *Best Pract Res Clin Rheumatol* 2002; 16: 347-60.
5. PACKHAM JC, HALL MA: Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. *Rheumatology* (Oxford) 2002; 41: 1428-35.
6. ZAK M, PEDERSEN FK: Juvenile chronic arthritis into adulthood: a long-term follow-up study. *Rheumatology* (Oxford) 2000; 39: 198-204.
7. WALLACE CA, RUPERTO N, GIANNINI E: Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol* 2004; 31: 2290-4.
8. PRINCE FH, OTTEN MH, VAN SUIJLEKOM-SMIT LW: Diagnosis and management of juvenile idiopathic arthritis. *BMJ* 2010; 341: c6434.

9. BEUKELMAN T, PATKAR NM, SAAG KG *et al*.: 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res* (Hoboken) 2011; 63: 465-82.
10. BARTOLI M, TARO M, MAGNI-MANZONI S *et al*.: The magnitude of early response to methotrexate therapy predicts long-term outcome of patients with juvenile idiopathic arthritis. *Ann Rheum Dis* 2008; 67: 370-4.
11. FLATO B, LIEN G, SMERDEL A *et al*.: Prognostic factors in juvenile rheumatoid arthritis: a case-control study revealing early predictors and outcome after 14.9 years. *J Rheumatol* 2003; 30: 386-93.
12. MAGNANI A, PISTORIO A, MAGNI-MANZONI S *et al*.: Achievement of a state of inactive disease at least once in the first 5 years predicts better outcome of patients with polyarticular juvenile idiopathic arthritis. *J Rheumatol* 2009; 36: 628-34.
13. OEN K, TUCKER L, HUBER AM *et al*.: Predictors of early inactive disease in a juvenile idiopathic arthritis cohort: results of a Canadian multicenter, prospective inception cohort study. *Arthritis Rheum* 2009; 61: 1077-86.
14. SPIEGEL LR, SCHNEIDER R, LANG BA *et al*.: Early predictors of poor functional outcome in systemic-onset juvenile rheumatoid arthritis: a multicenter cohort study. *Arthritis Rheum* 2000; 43: 2402-9.
15. WULFFRAAT N, VAN DER NET JJ, RUPERTO N *et al*.: The Dutch version of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ). *Clin Exp Rheumatol* 2001; 19 (Suppl. 23): S111-5.
16. DEMPSTER H, POREPA M, YOUNG N, FELDMAN BM: The clinical meaning of functional outcome scores in children with juvenile arthritis. *Arthritis Rheum* 2001; 44: 1768-74.
17. ADIB N, HYRICH K, THORNTON J *et al*.: Association between duration of symptoms and severity of disease at first presentation to paediatric rheumatology: results from the Childhood Arthritis Prospective Study. *Rheumatology* (Oxford) 2008; 47: 991-5.
18. HYRICH KL, LAL SD, FOSTER HE *et al*.: Disease activity and disability in children with juvenile idiopathic arthritis one year following presentation to paediatric rheumatology. Results from the Childhood Arthritis Prospective Study. *Rheumatology* (Oxford) 2010; 49: 116-22.
19. NORDAL E, ZAK M, AALTO K *et al*.: Ongoing disease activity and changing categories in a long-term nordic cohort study of juvenile idiopathic arthritis. *Arthritis Rheum* 2011; 63: 2809-18.
20. OEN K, DUFFY CM, TSE SM *et al*.: Early outcomes and improvement of patients with juvenile idiopathic arthritis enrolled in a Canadian multicenter inception cohort. *Arthritis Care Res* (Hoboken) 2010; 62: 527-36.
21. WALLACE CA, HUANG B, BANDEIRA M, RAVELLI A, GIANNINI EH: Patterns of clinical remission in select categories of juvenile idiopathic arthritis. *Arthritis Rheum* 2005; 52: 3554-62.
22. HEILIGENHAUS A, NIEWERTH M, GANSER G, HEINZ C, MINDEN K, GERMAN UVEITIS IN CHILDHOOD STUDY G: Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. *Rheumatology* (Oxford) 2007; 46:1 015-9.
23. RINGOLD S, SEIDEL KD, KOEPSELL TD, WALLACE CA: Inactive disease in polyarticular juvenile idiopathic arthritis: current patterns and associations. *Rheumatology* (Oxford) 2009; 48: 972-7.
24. MARTINI A, LOVELL DJ: Juvenile idiopathic arthritis: state of the art and future perspectives. *Ann Rheum Dis* 2010; 69: 1260-3.
25. RAVELLI A, VARNIER GC, OLIVEIRA S *et al*.: Antinuclear antibody-positive patients should be grouped as a separate category in the classification of juvenile idiopathic arthritis. *Arthritis Rheum* 2011; 63: 267-75.
26. SCOTT C, MEIORIN S, FILOCAMO G *et al*.: A reappraisal of intra-articular corticosteroid therapy in juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2010; 28: 774-81.
27. ALBERS HM, WESSELS JA, VAN DER STRAATEN RJ *et al*.: Time to treatment as an important factor for the response to methotrexate in juvenile idiopathic arthritis. *Arthritis Rheum* 2009; 61: 46-51.
28. VAN ROSSUM MA, VAN SOESBERGEN RM, BOERS M *et al*.: Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. *Ann Rheum Dis* 2007; 66: 1518-24.
29. BROOKS CD: Sulfasalazine for the management of juvenile rheumatoid arthritis. *J Rheumatol* 2001; 28: 845-53.
30. VAN ROSSUM MA, FISELIER TJ, FRANSSEN MJ *et al*.: Sulfasalazine in the treatment of juvenile chronic arthritis: a randomized, double-blind, placebo-controlled, multicenter study. Dutch Juvenile Chronic Arthritis Study Group. *Arthritis Rheum* 1998; 41: 808-16.
31. HUANG JL, CHEN LC: Sulphasalazine in the treatment of children with chronic arthritis. *Clin Rheumatol* 1998; 17: 359-63.
32. IMUNDO LF, JACOBS JC: Sulfasalazine therapy for juvenile rheumatoid arthritis. *J Rheumatol* 1996; 23: 360-6.
33. VAN DER MEER A, WULFFRAAT NM, PRAKKEN BJ, GIJSBERS B, RADEMAKER CM, SINNEMA G: Psychological side effects of MTX treatment in juvenile idiopathic arthritis: a pilot study. *Clin Exp Rheumatol* 2007; 25: 480-5.
34. BULATOVIC M, HEIJSTEK MW, VERKAAIK M *et al*.: High prevalence of methotrexate intolerance in juvenile idiopathic arthritis: development and validation of a methotrexate intolerance severity score. *Arthritis Rheum* 2011; 63: 2007-13.
35. DAMASIO MB, MALATTIA C, MARTINI A, TOMA P: Synovial and inflammatory diseases in childhood: role of new imaging modalities in the assessment of patients with juvenile idiopathic arthritis. *Pediatr Radiol* 2010; 40: 985-98.
36. MALATTIA C, DAMASIO MB, MAGNAGUAGNO F *et al*.: Magnetic resonance imaging, ultrasonography, and conventional radiography in the assessment of bone erosions in juvenile idiopathic arthritis. *Arthritis Rheum* 2008; 59: 1764-72.